Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the applications.

Listing of Claims:

Claims 1-13 (Canceled).

14. (Currently amended) A method for making a derivative of hyaluronic acid, comprising the steps of:

a) forming an activated ester at a carboxylate of a glucuronic acid moiety of hyaluronic acid; ~~and~~

b) substituting at the carbonyl carbon of the activated ester formed in step (a), a side chain comprising a nucleophilic portion and a functional group portion such that the degree of substitution is more than 5%; and

c) forming a cross-linked hydrogel from the hyaluronic acid derivative.

15. (Currently amended) The method of claim 14, wherein the nucleophilic portion is selected from the group consisting of ammonia, primary amine, and secondary amine~~, hydroxyl, and sulfhydryl~~.

16. (Original) The method of claim 14, wherein the functional group portion is selected from the group consisting of active ester, aldehyde, amine, arylazide, hydrazide, maleimide, sulfhydryl, and peptide.

17. (Original) The method of claim 14, wherein step (a) is performed with an active ester selected from the group consisting of a substituted triazole, N-sulfosuccinimide, nitrophenol, partially halogenated phenol, perhalophenol, pentafluorophenol, HOBT, and NHS, by carbodiimide-mediated coupling.

18. (Canceled).

19. (Currently amended) A method for forming a matrix for a temporary scaffold for tissue repair according to the method of claim 14 ~~18~~, wherein a crosslinker is used in step c), and wherein the crosslinker is selected from the group consisting of polyvalent active ester, aldehyde, amine, arylazide, maleimide, and sulfhydryl.

20. (Currently amended) A method for forming a matrix for a temporary scaffold for tissue repair according to the method of claim 14 ~~18~~, wherein the HA derivative comprises a peptide substrate for transglutaminase, and wherein the HA derivative is crosslinked using transglutaminase.

21. (Currently amended) The method of claim 14 ~~18~~, wherein step (c) is performed in the presence of cells.

22. (Currently amended) The method of claim 14 ~~18~~, wherein step (c) is performed in the presence of at least one member selected from the group consisting of growth factors, cytokines, drugs, and bioactive peptides.

23. (Currently amended) The method of claim 22, wherein the bioactive peptide ~~is~~ RGD is present.

24. (Currently amended) The method of claim 22, wherein ~~the~~ -- a -- bioactive peptide is present and is a substrate for transglutaminase.

25. (Currently amended) The method of claim 24, wherein the bioactive peptide ~~is~~ APQQEA is present.

26. (Currently amended) The method of claim 24, wherein the growth factor ~~is~~ TGF-β or BMP is present.

27. (Currently amended) The method of claim 14 ~~18~~, wherein step (c) is performed *in situ* in a patient in need of tissue repair.

28-39. (Canceled).

Claim Amendments

Applicants have amended the claims as follows:

Applicants have amended claim 14 to recite "such that the degree of substitution is more than 5%" and "c) forming a cross-linked hydrogel from the hyaluronic acid derivative."

Claim 15 has been amended to no longer recite hydroxyl and sulfhydryl.

Please cancel claim 18, without prejudice.

Claims 19-22 and 27 have been amended to depend from claim 14 instead of claim 18.

Claims 23-26 have been amended for purposes of clarity.

None of these amendments adds new matter to the application.

Remarks

The Amendments

Applicants have amended claim 14 to recite "such that the degree of substitution is more than 5%." Support for this amendment can be found in the specification at page 29: "[a] degree of modification of 10-25% yielded efficient cross-linking but also a molecule that would still be recognized by glycosidases and by HA receptors as HA and thus allow for recognition and processing of the material by cells []." Further support can be found in the specification at pages 12-14, wherein, *inter alia*, "optimally modified" HA is described as having "~20-25%" modification.

Applicants have also amended claim 14 to recite step "c) forming a cross-linked hydrogel from the hyaluronic acid derivative." Step c) is from claim 18, which applicants have canceled.

Claim 15 has been amended to no longer recite hydroxyl and sulfhydryl, as suggested by the Examiner.

Applicants have canceled claim 18, without prejudice. The limitation of claim 18 has been added to claim 14.

Claim 19 has been amended to recite that "a crosslinker is used in step c), and wherein."

Claims 19-22 and 27 have been amended to depend from claim 14 instead of claim 18.

Claims 23-26 have been amended for purposes of clarity, as suggested by the Examiner.

None of these amendments adds new matter to the application.

Information Disclosure Statement

The Examiner has indicated that certain prior art documents submitted in the parent application were unavailable. Applicants re-submit herewith a copy of the documents in question, together with a copy of the March 8, 2004 Information Disclosure Statement and PTO Form 1449. Applicants request that the Examiner consider all of the documents listed and return a copy of Form 1449 with the documents acknowledged as considered.

Rejections Under 35 U.S.C. § 112

The Examiner has rejected claims 14-27 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that step b) of claim 14 appears to require a product that has a side chain attached to the carbonyl carbon which, after the reaction, comprises both a nucleophilic group and some other functional group. The Examiner further states that, in the

example of ammonia as the nucleophilic group per claim 15, it is not clear how ammonia is meant to be bonded to the side chain.

In the interest of expediting prosecution of the application, applicants have amended claim 15 to delete reference to "hydroxyl" and "sulfhydryl," as suggested by the Examiner.

Claim 19 has been amended to recite that "a crosslinker is used in step c), and wherein," so as to provide proper antecedent basis, as suggested by the Examiner.

Claims 23-26 have been amended, as suggested by the Examiner, for reasons of clarity.

Rejections under 35 U.S.C. § 102 (e)

Miller et al.

The Examiner has rejected claims 14-19 under 35 U.S.C. § 102 (e) as being anticipated by United States patent 6,174,999 ("Miller et al."). Applicants traverse.

The claims, as amended, require a degree of substitution of more than 5%. Nowhere in Miller et al. does it indicate that there is a degree of substitution of more than 5%.

Also, it appears that the Examiner is saying that Miller et al. inherently anticipates the limitation requiring crosslinking. The standard for inherency, however, requires an unambiguous conclusion that the limitation is present in the prior art reference. It is ambiguous as to whether or not the molecules of Miller et al. were crosslinked. For this additional reason, Miller et al. does not anticipate.

Waki et al.

The Examiner has rejected claims 14, 15, 17 and 18 under 35 U.S.C. § 102 (e) as being anticipated by United States patent 6,025,444 ("Waki et al."). Applicants traverse.

Waki et al. also does not disclose a degree of substitution of more than 5%. See Waki et al. Figures 2-4, 7-8 and column 11, lines 38-47.

Righetto et al.

The Examiner has rejected claims 14-16 under 35 U.S.C. § 102 (e) as being anticipated by United States patent 5,856,299 ("Righetto et al."). Applicants traverse.

Righetto et al. does not anticipate applicants' claims explicitly or inherently. Righetto et al. teaches neither crosslinking agents nor that homo-crosslinking occurs as a result of its method. Righetto et al. states that "[s]urprisingly, active esters of carboxy polysaccharides and their semisynthetic derivatives have been obtained **without any undesired side reactions, such as the formation of intra- and inter-chain bridges, which lead to the phenomenon known as auto-crosslinking.**" Righetto et al. at col. 4, lines 45-49 (emphasis added).

The formation of the "gelatinous slab" in Example 17 of Righetto et al., is likely to involve only hydrogen bonding between HA chains, not covalent bonding at the introduced functional group, because "water vapour is used as a coagulant" (Righetto et al. at col. 11, lines 60-63). This is not the covalent crosslinking of HA chains via functional groups introduced at the carboxyl group of HA that is taught and claimed in the instant application. Thus, applicants' claimed invention is not "inherent" in any Righetto et al. composition.

Inherent anticipation "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." Rapoport v. Dement, 59 USPQ2d 1215, 1222 (Fed. Cir. 2001) (emphasis in original) (citations omitted). Because Righetto et al. neither teaches nor inherently discloses covalently crosslinked HA chains, it cannot anticipate the invention of amended claims 14-16.

Rejections under 35 U.S.C. § 102 (b)

Akima et al.

The Examiner has rejected claims 14-17 under 35 U.S.C. § 102 (b) as anticipated by EP 506976 ("Akima et al."). Applicants traverse.

Akima et al. is only concerned with attaching active agents to HA, not with making hydrogels or crosslinking. It therefore does not disclose these required elements of the amended claims, nor does it disclose the degree of substitution of its molecules. For these reasons, Akima et al. does not anticipate.

Guire et al.

The Examiner has rejected claims 14-19 under 35 U.S.C. § 102 (b) as being anticipated by United States patent 5,512,329 ("Guire et al."). Applicants traverse.

Guire et al., concerning "substrate surface preparation," does not disclose a degree of substitution of its molecules of more than 5%, nor the required crosslinking of the amended claims. Therefore Guire et al. does not anticipate.

Rejections under 35 U.S.C. § 103 (a)

Miller et al.

The Examiner has rejected claims 14-19 and 22-26 under 35 U.S.C. § 103 (a) as obvious in view of Miller et al. Applicants traverse.

As noted above, Miller et al. does not contain the degree of substitution or crosslinking limitations of the amended claims. Nor is there a suggestion in Miller et al. that fills in these gaps. One of skill in the art would not have been motivated to crosslink the molecules of

Miller et al., nor would they have had a reasonable expectation of successfully achieving the degree of substitution claimed by applicants.

Miller et al. In View Of Prestwich et al.

The Examiner has rejected claims 14-19 and 22-26 under 35 U.S.C. § 103 (a) as obvious over Miller et al. in view of United State patent 5,874,417 ("Prestwich et al."). Applicants traverse.

As noted above, Miller et al. does not contain the degree of substitution or crosslinking limitations of the amended claims. Nor is there a suggestion in Prestwich et al. that fills in these gaps. One of skill in the art would not have been motivated to crosslink the molecules of Miller et al., nor would they have had a reasonable expectation of successfully achieving the degree of substitution claimed by applicants. As noted by the Examiner, Prestwich et al. does not perform the derivatization of HA according to the present invention. The Examiner has not provided a motivation for one of skill in the art to combine these two references. Nor is there a reasonable expectation that employing the method of Miller et al. will result in crosslinked hydrazido groups of Prestwich et al.

Miller et al. In View Of Stedronsky et al.

The Examiner has rejected claims 14-19 and 22-26 under 35 U.S.C. § 103 (a) as obvious over Miller et al. in view of United State patent 5,817,303 ("Stedronsky et al."). Applicants traverse.

As noted above, Miller et al. does not contain the degree of substitution or crosslinking limitations of the amended claims. Nor is there a suggestion in Stedronsky et al. that fills in these gaps. Nothing in Stedronsky et al. points to Miller et al. nor does anything in Miller et al. point to Stedronsky et al. One of skill in the art would not have been motivated to

crosslink the molecules of Miller et al., nor would they have had a reasonable expectation of successfully achieving the degree of substitution claimed by applicants. The Examiner has not provided a motivation for one of skill in the art to combine these two references.

Rhee et al. In View Of Righetto et al.

The Examiner has rejected claims 14-16, 18, 19 and 21-27 under 35 U.S.C. § 103 (a) as obvious over United States patent 5,510,418 ("Rhee et al.") in view of Righetto et al. Applicants traverse.

The Examiner has not made out a *prima facie* case of obviousness, as is required by section 2142 of the MPEP. None of the cited references contain the suggestion, alone or together, to create the claimed invention.

As discussed above, Righetto et al. does not suggest the crosslinking step, as is required by applicants' amended claims. There is no teaching that the gelatinous slab of Righetto et al. involves covalent crosslinking of the introduced functional groups of HA. In fact, Righetto et al. teaches that its derivatives avoid the problem of "auto-crosslinking" at introduced functional groups. Because Righetto et al. teaches away from the benefits of crosslinking, one of skill in the art would not have been motivated to combine this reference with Rhee et al.

For the same reason, one of skill in the art reading Rhee et al. would not be motivated to employ the methods of Righetto et al.

Furthermore, the crosslinking methods of the prior art, including those cited in Rhee et al., are completely different from those disclosed in the instant application. The ester, urethane and ether-induced crosslinking disclosed most likely target the **hydroxyl groups** instead of the carboxyl groups of HA. These are relatively nonspecific reactions that result in the formation of a number of different reactive intermediates which then react further. Because of

this, the exact structure of the reaction products is unpredictable. Such reactions typically lead to a loss of native polysaccharide structure and/or cleavage of the polysaccharide chains with a concomitant loss of the unique properties of HA. In any event, the mechanisms suggested for HA crosslinking reactions in the Rhee et al. patent are not those of applicants' invention.

Because of the problems associated with these prior art crosslinking methods, applicants set out to develop the crosslinking methods described in the instant application. In applicants' compositions, derivatized carboxyl groups are crosslinked to form predictable and stable products without affecting the structure or length of the polysaccharide chains. While the notion of forming a gel-like materials by crosslinking a hydrophilic polymer was in the prior art, methods of predictably crosslinking HA while at the same time essentially preserving its structure were not.

Thus there is no teaching or suggestion in Rhee et al. to use the HA derivatization method of Righetto et al., nor is there a teaching or suggestion in Righetto et al. to use the crosslinking agents of Rhee et al.

Rhee et al. In View Of Righetto et al.

The Examiner has rejected claims 14-16 and 18-27 under 35 U.S.C. § 103 (a) as obvious over Rhee et al. and Righetto et al. in view of United States patent 5,270,300 ("Hunziker") and Hohenadl et al. Applicants traverse.

For the reasons stated above, one of skill in the art would not be motivated to combine the Rhee et al. and Righetto et al. references. The disclosures of Hunziker and

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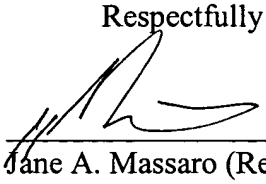
* Applicants refer to the June 16, 2000 Declaration of Daniel Aeschlimann under 37 C.F.R. * 1.132, filed with applicants* Reply of June 16, 2000, to provide support for certain of applicants* assertions. A copy of this Declaration is provided herewith.

Hohenadl et al., which are cited for their disclosure of use of transglutaminase, do not provide the missing suggestion to crosslink the particular HA derivatives according to the claimed methods with the claimed degree of modification. There is simply nothing in the Hunziker and Hohenadl et al. references that suggests the combination of the claimed features.

Conclusion

For the above reasons, applicants request that the Examiner withdraw her rejections and allow the currently pending claims to issue.

Respectfully submitted,



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